M & I
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DISSERTATION SEMINAR

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"The SecA2 pathway of *Mtb* exports effectors that work in concert to arrest phagosome maturation"

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Abstract

Kate Zulauf: The SecA2 pathway of *Mtb* exports effectors that work in concert to arrest phagosome maturation
(Under the direction of Miriam Braunstein)

In order to promote disease, *Mycobacterium tuberculosis* exports proteins outside of the bacterial cell into the host environment where the proteins can interfere with host defense mechanisms such as phagosome maturation. The SecA2 pathway is one system *M. tuberculosis* utilizes to export such proteins. SecA2 is a non-essential specialized SecA ATPase required for exporting a relatively small subset of proteins. The SecA2 pathway, although not essential for growth of *M. tuberculosis* in vitro, is required for virulence of *M. tuberculosis*. The requirement for SecA2 during infection suggests that SecA2 and its exported effectors play important roles in *M. tuberculosis* pathogenesis. Therefore, we set out to both identify *M. tuberculosis* proteins that are exported by the SecA2 pathway and identify functions of SecA2 in *M. tuberculosis* virulence. Using quantitative proteomics, we identified solute binding proteins and Mce proteins as two classes of proteins exported by SecA2 as well additional proteins of unknown function that may account for the role of SecA2 in virulence. We additionally investigated the function of the SecA2 pathway in phagosome maturation arrest which is critical for *M. tuberculosis* replication and pathogenesis, by identifying and investigating proteins exported by the SecA2 pathway that play essential roles in this process. Work presented in this dissertation shows that SecA2 exports two effectors of phagosome maturation arrest: SapM and PknG. We further show that the role of SecA2 in exporting these effectors contributes to phagosome maturation arrest and growth of *M. tuberculosis* in macrophages. Finally, to further elucidate the functions and mechanisms of the SecA2 export pathway of *M. tuberculosis* beyond phagosome maturation arrest, we utilized genome-wide genetic interaction mapping of *secA2*. Our results expand our understanding of the SecA2 pathway by identifying candidate substrates and components of the export machinery and by revealing roles for SecA2 in *M. tuberculosis* processes involving transporters, phosphate import, copper resistance, peptidoglycan synthesis, and lipid metabolism and homeostasis. Taken together, the findings presented in this dissertation have significantly advanced our understanding of the roles of the SecA2 export pathway in the virulence of *M. tuberculosis*.